HEART VALVE AREA CALCULATIONS: EFFECTS OF EXERCISE AND CATECHOLAMINE INFUSION

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by

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After early attempts at surgically ameliorating acquired heart valve lesions had faltered, renewed activity in the late 1940's led to perfection of techniques whereby surgeons began to achieve symptomatic relief and prolonged life in patients with mitral stenosis.[1-3] Initially, only hopelessly disabled patients refractory to all standard treatment received the operation, which involved a blind incision of the fused mitral commissures after surgically entering the left atrium. Even with respect to these gravely ill patients, investigators realized that certain features of their disease appeared to predict the likelihood of a good surgical result. As the operation was extended to those less severely affected, it became particularly important to learn what patients might be expected to benefit from such a major operation.

Various groups sought to define specifically and objectively those clinical and laboratory parameters that enabled one to assess the desirability of surgery in a patient with mitral valve disease, and equally important, to assess the outcome by other than subjective means. Given the profound impairment suffered by these first few patients who volunteered for such pioneering surgery, there existed an understandable tendency for some who survived to exaggerate their symptomatic relief, making analysis of the surgical results difficult.

Unfortunately, precise methods of evaluation were lacking,

as were criteria with which to interpret the results of whatever evaluation was undertaken. One group advised that preoperative screening should consist of "a careful clinical history and examination ... by an especially interested cardiologist."[2] Echoing this sentiment, another report stated that "it is obvious that the careful auscultatory examination by an experienced cardiologist is paramount."[4] Although such careful examinations served the necessary function of documenting the existence of the disease that one sought to treat, it became clear that such maneuvers provided limited information and more elaborate means soon surfaced to delineate the nature of the cardiac disease and the prospects for surgical relief.

With increasing surgical experience, surgeons discovered that operative relief could obtain only in those patients whose symptoms stemmed predominantly from a mechanical mitral "block," that is , a stenotic valve which obstructed flow. If other cardiac disorders, such as myocardial dysfunction, bacterial endocarditis, active rheumatic carditis, and mitral regurgitation, or non-cardiac factors contributed to the patient's symptom complex, surgery offered little benefit and substantial risk. Hence, one tried to exclude the presence of these cardiac and non-cardiac factors in selecting patients for surgery. In addition to the history and physical examination, sometimes repeated throughout long periods of observation, blood cultures, electrocardiograms, standard chest roentgenograms, four-way radiologic views of the heart with barium swallow, and phono-

cardiograms were utilized in efforts at complete diagnosis.[4-7] For example, left ventricular enlargement or hypertrophy documented by these methods implied additional cardiac defects, and reduced the probability that surgical correction of the mitral stenosis would yield a good outcome.

Although one early observation held that intra-cardiac catheterization was possibly helpful in only "certain confusing states of mitral stenosis,"[8] its use preoperatively became quickly established because of the additional valuable information it provided about the severity of a suspected mitral block. By performing right-sided catheterizations, one obtained pulmonary artery pressures and indirect left atrial pressures (by a pulmonary capillary wedge catheter). Studies had shown that patients with symptomatic mitral stenosis had varying degrees of pulmonary artery hypertension, abnormal resting cardiac outputs, and abnormal cardiac output responses to exercise.[9] Catheterization permitted quantitative measurements of these parameters, and furthermore, allowed pre- and post-operative comparisons by repeat cath study. In this way, researchers learned that post-op relief of symptoms generally correlated with a reduction in pulmonary pressures, although rarely did such pressures fall to a normal range.

In screening candidates for operation, it was felt that surgery offered little relief to patients with no pulmonary hypertension, with or without aberrant cardiac outputs. In such cases, factors other than mitral block were thought to

be responsible for symptoms. Investigators sometimes employed acute digitilization of patients undergoing catheterization in order to discern whether myocardial insufficiency played a role in the production of abnormal pulmonary artery pressures and cardiac outputs.[10]

One group advocated that study of the morphology of the indirect left atrial pressure curve yielded further information about the presence of mitral regurgitation complicating mitral stenosis. Excessive regurgitation precluded surgical repair of the valve. Others criticized the value of pressure curve analysis.[11, 12]

Despite these advances in identifying more precisely those factors relevant to an evaluation of the suspected stenosis, certain problems remained. One problem was that hemodynamic measurements at cath reflected the particular physiologic state of the patient at that moment in time, and did not necessarily bear a relationship to the hemodynamic status of the patient when he was symptomatic, or at another time when the catheterization was repeated. In other words, the degree of pulmonary hypertension not only depended on the existence of some pathology, but also on the uncharacterized and uncontrolled inotropic, chronotropic, and vascular tonal influences present at a given time. Did an anxious patient with a heart rate of 120 and a mean pulmonary artery pressure of 30 mm Hg have a more severe block than a patient with a rate of 75 and a pressure of 25 mm Hg? Furthermore, as investigators noted, pulmonary hypertension did

not specify mitral stenosis, but potentially resulted from other lesions as well. Even if one was certain that a mitral block alone produced the pulmonary hypertension, the correlation between the pressure measured and the severity of the stenosis was uncertain. As already pointed out for example, pulmonary hypertension persisted in those patients who experienced subjective relief with commisurotomy, albeit usually at a reduced level.

Preoperative evaluation of these patients was satisfactorily refined when it became possible to measure the actual area of the stenotic valve. Borrowing principles from hydraulic engineering, Gorlin and Gorlin developed a method permitting a quantitative assessment of the severity of stenotic valve lesions. By concentrating on the valve area, these authors focused on the essential problem of obstruction to flow, rather than on variable effects secondary to the obstruction such as pulmonary hypertension.[13]

Their initial insight into the problem was that the non-laminar flow through a valve was inadequately described by Poisseuille's Law : $\text{Flow} = \frac{(\text{Pressure Gradient})(\text{Radius})^4}{(\text{Length})(\text{Fluid Viscosity})}$

Hydraulic considerations suggested that flow through a valve was more closely approximated by Torricelli's orifice equation:

Flow = $C_c \cdot A \cdot V$, Where A is the orificial area, V is the flow velocity, and C_c is the coefficient of contraction, a constant. A second applicable physical principle stated that the square of the flow velocity, V^2, = $C_v 2 \cdot 2 \cdot gh$, where g is gravitational

acceleration, 980cm/sec^2, h is the pressure gradient, and C_{v2} is the coefficient of velocity, a constant. Rearranging the two equations and solving for area yielded a formula for valve area: $\text{Area} = \frac{\text{Valve Flow}}{C_c \cdot C_{v2}\sqrt{2gh}} = \frac{\text{Valve Flow}}{44.5 \cdot C\sqrt{h}}$

where $C = C_c \cdot C_{v2}$.

To use the formula for mitral valve calculations, valve flow was based on an adjustment of cardiac output which reflected the fact that mitral valve flow was a diastolic event. Hence, mitral valve flow (in ml/sec) = cardiac output in ml/min divided by the diastolic filling period (DFP) in sec/min.

Gorlin and coworkers then applied this hydraulic formula to the intact heart. Routine catheterization techniques of the time did not include direct measurement of left heart pressures, and so the DFP was estimated from the systolic ejection time, SEP (DFP = 60 - SEP). This produced a slightly exaggerated value for DFP, since it incorporated both the systolic isovolumic phases as well as the diastolic filling period. Furthermore, pressure gradients across the mitral valve were approximated as the difference between the mean pulmonary capillary wedge pressure as an indirect measurement of left atrial pressure, and 5 mm Hg, a number chosen to represent the average left ventricular diastolic pressure. Given these assumptions, it was found through testing of surgical and autopsy specimens that the proper constant needed to determine the mitral valve area (C) was 0.7.[13]

Further studies explored the application of the formula

to the stenotic aortic valve, although at the time, surgical correction of that lesion had not proved nearly as successful as the mitral operation.[14] When aortic valve flow (computed as the cardiac output divided by the systolic ejection period) and aortic valve gradients were inserted into the formula, the proper constant for area calculation was found to be 1.0.[15]

Gorlin and colleagues cogently demonstrated how their particular analysis more readily defined the clinical severity of stenotic lesions and the possible benefits of surgery than the methods suggested by others. Studies had shown that symptoms attributable to mitral stenosis included those resultant from high left atrial pressures, inducing pulmonary hypertension, and diminished caridac output.[5,6,9,10]

Because of the mitral block, the transvalvular gradient needed to produce flow across the valve resulted in an elevated left atrial pressure, manifesting itself as dyspnea secondary to pulmonary congestion, or worse, as pulmonary edema. Later in the course, right heart deterioration resulted from the increased pulmonary resistance. Patients also experienced exercise intolerance or easy fatiguability as a result of abnormal cardiac outputs at rest and/or on attempted exercise. Although one could measure both outputs and left atrial pressures at catheterization, one still needed to know how to interpret these data.

The Gorlin formula incorporated these elements and revealed

their inter-relationship, which other researchers had failed to make use of in their analyses. No matter what the patient's inotropic and chronotropic state, the level of peripheral vascular resistance, or the degree of primary myocardial disease, he existed hemodynamically at a point of a curve described by the formula, which allowed only certain pairings of pressures with cardiac outputs at a given valve area. This invariable relationship provided the key with which to understand for example, whether a patient with a low normal cardiac output of 3.0 l/min had a clinically more severe lesion than a patient with an output of 4.0 l/min.

The Gorlin formula demonstrated that any compensatory mechanism operating in vivo which decreased pathologic left-sided pressures also had to lower cardiac output, the valve flow time period or both. Inversely, any increase in cardiac output reflected in increased valve flow, as might be induced with exercise, necessitated a rise in those pressures. Thus, in a particular patient, the formula explained how the normal cardiac output obtained at cath may have been possible only at the price of an elevated mitral valve gradient. Similarly, a particular patient with severe mitral stenosis might have been found to have a relatively normal left atrial pressure by maintenance of a low cardiac output.

Therefore, the formula emphasized that it was the fixed relationship of flows to gradients and not the flows and gradients themselves which mattered, and this relationship could be

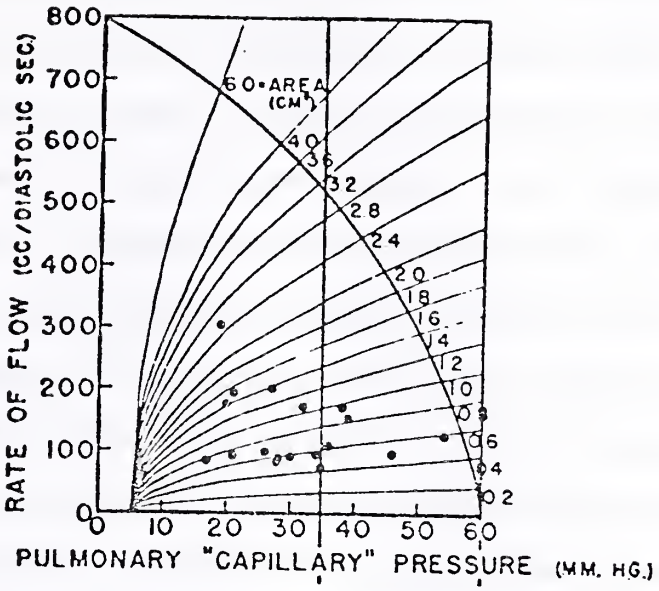

Figure 1

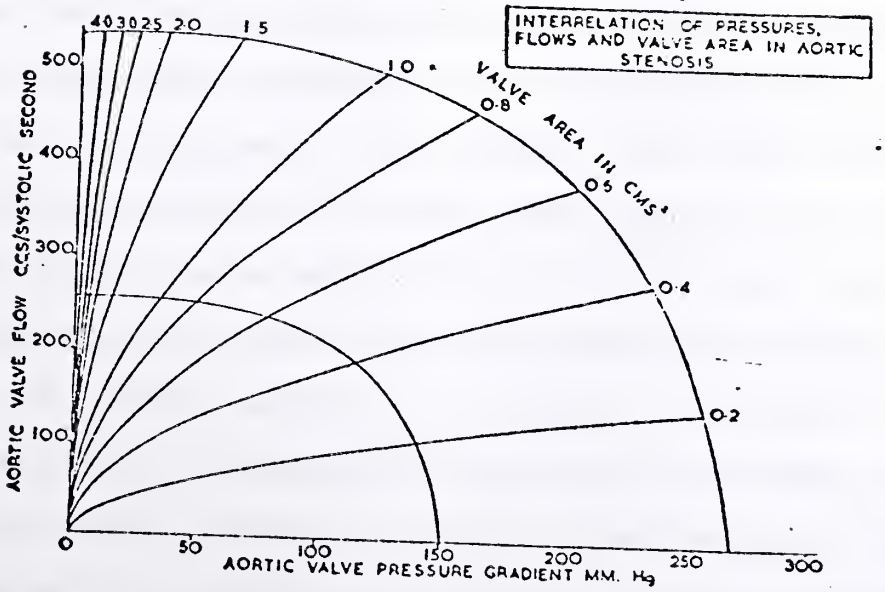

Figure 2

(See reference 16)

summarized by the valve area, which was a function of both parameters. Gorlin and coworkers then proceeded to define on physiologic grounds what lesions constituted clinically severe disease and merited operative relief. As illustrated in Figures 1 and 2, a given valve area generated a specific pressure-flow curve. Examining these graphs, Gorlin and colleagues recognized that at "critical" areas, the curves flattened. A flat region of the curve implied that any increase in transvalvular pressure, large or small, brought about only a relatively minimal increase in flow. Indeed, even to produce minimal increments in flow, large increases in pressure were necessary. For the mitral valve, this adverse situation obtained at about 1.0 to 1.2 cm^2 or less; similarly for the aortic valve, at about 0.5 to 0.6 cm^2.

At these critical areas, any increased demand on cardiac performance invariably exacted a high price, even if resting values measured at catheterization suggested only slightly aberrant hemodynamic parameters, and one could predict a severe functional impairment. For example, one could see that a resting wedge pressure of 15 mm Hg was possible in a patient with a MVA (mitral valve area) of only 1.0 cm^2, but only if his mitral valve flow (MVF) was 100 ml/sec, which might correspond to a low cardiac output of 2.5 l/min. Yet merely to double that MVF required a lengthening of the DFP (and thereby required a decreased SEP) and/or as much as a quadrupling of the wedge pressure (to a dangerous 60 mm Hg). One did not actually have to

record these forbidding observations at catheterization to know that these relationships held. On the other hand, a patient with a valve area of 2.0 cm^2 could have had a higher MVF of 200 ml/sec with the same wedge pressure of 15 mm Hg. The functional impairment induced by this patient's stenosis was obviously much less. Indeed, he might have been able to treble the MVF of 100 ml/sec before experiencing any respiratory difficulties (a MVF of 300 ml/sec would yield a left atrial pressure gradient of about 26 mm Hg). One expected the first patient to benefit much more from a surgical procedure than the second.[17]

Although the mechanics of myocardial compromise were somewhat different in aortic stenosis (involving symptoms secondary to left ventricular hypertrophy and inadequacy of myocardial oxygenation, as well as to pulmonary congestion), similar considerations argued for the utility of the critical aortic valve area in selecting patients for aortic valve replacement when that operation became available.

The theoretical advantages of the Gorlin approach were clear, but was the formula reliable? Did hydraulic principles prove to be adaptable to living systems? Gorlin and Gorlin noted some of the theoretical problems with their equation.[13] For example, the equations used to derive the formula were best applicable to constant velocity flow, not the pulsatile flow of blood. Furthermore, the turbulence generated in pulsing the blood across the valve altered the constancy of

C_C and C_{V2}, each in different directions. Finally, as noted above some of the parameters to be plugged into the formula could not even be measured, but were estimated (i.e., gradient and DFP). Nonetheless, Gorlin and Gorlin found agreement between the calculated valve area and empirically determined valve area in three of eleven patients; five calculated areas exceeded measured valve areas by 0.1 cm^2, and three calculated areas were 0.1 to 0.2 cm^2 less than empirically determined valve areas.[13]

Examining the equation by means of a theoretical model, Rodrigo added that even the actual orifice area and the cross-sectional areas of the chambers emptying into and draining the orifice influenced the accuracy of the formula, factors not appraised in calculating valve area. Yet he basically affirmed that the formula held for the conditions which pertained to human subjects undergoing catheterization.[18]

There have been subsequent critical comments concerning the formula, suggesting that it could be made more precise by modifying the valve constant to reflect current cath techniques which no longer require estimations of DFP and gradients.[19, 20] The proposed modification has been a minor one and has not directly borne on the matter of the consistency of the formula when applied to a variety of hemodynamic settings, since it has concerned the constant, not the dependent variables.

Certain technical problems have remained with respect to the effects of cath-derived data on the validity

of the formula. The accuracy of the formula has of course absolutely depended on the ability to measure the necessary hemodynamic parameters precisely. Has random or systematic error in catheterization measurements, consequent of the way in which flows and gradients were recorded, posed an obstacle to the precision of valve area calculations? Have the low recorded flows and gradients, as sometimes found in valvular heart disease particularly lent themselves to distortion of calculated areas?[21] Because the Gorlin formula incorporated a mathematical division, a small error in the denominator (i.e., the gradient determined at cath) potentially created a large error in the valve area.

For example, a patient with a mitral valve gradient (MVG) of only 6 mm Hg and a mitral valve flow of 137 ml/sec could have a MVA of 1.8 cm^2. An error in gradient measurement of a mere 7.5 mm Hg, yielding a MVG of 13.5 mm Hg (6 + 7.5 = 13.5), would have resulted in a calculated critical valve area of 1.2 cm^2. Another illustration - if a patient's MVF equals 90 ml/sec and MVG 2mm Hg, one calculates a MVA of 2.1 cm^2. Yet a slight imprecision in MVG measurement yielding a value of 6 mm Hg, a difference of only 4 mm Hg, would have given a critical area of 1.2 cm^2.

Another technical problem in utilizing the formula has concerned the accuracy of transvalvular flow determinations. The method employed for cardiac output measurement (described in further detail in the Methods and Materials section), the

direct Fick oxygen consumption technique, is based on the following:

$$\text{Cardiac Output} = \frac{\text{Total Body Oxygen Consumption}}{\text{arterial } O_2 \text{ content} - \text{mixed venous } O_2 \text{ content}} \quad (22)$$

In other words, because of its role in distributing oxygen to oxygen consuming tissues of the body, one is able to deduce the total cardiac flow from knowing the total oxygen consumption and the arterio-venous oxygen difference. The method itself has been reproducible in a given patient ±10%, a variability unlikely to cause significant imprecision in the calculated valve area.[22,23] However, a problem has arisen in patients with left heart regurgitant lesions as well as stenosis, because in these patients, the Fick method has underestimated transvalvular flow to a degree depending on the severity of the regurgitation. The inadequacy of the output method in these patients has stemmed from the fact that the Fick principle measured only that fraction of total oxygen carrying blood flow supplying the body's oxygen consuming tissues. This oxygen is contained in the blood ejected from the left heart (the forward flow). In the setting of regurgitant lesions, part of total left ventricular oxygen carrying flow never leaves the heart to reach oxygen consuming tissues, but regurgitates back into the heart (regurgitant flow). Hence, the Fick method measures only forward flow, but in patients with regurgitant lesions, transvalvular flow depends on the sum of forward and regurgitant flow. To illustrate, a patient has mitral stenosis and aortic regurgitation. The totality of blood flow crosses

the mitral valve, enters the left ventricle, and leaves this chamber during systolic contraction. During diastole, a fraction of this blood drains back into the left ventricle, the rest continuing forward to perfuse the body. The Fick method measures only this forward fraction. One can see that the total transvalvular flow has consisted of both blood flowing forward and regurgitating through the aortic valve. Therefore, the Fick method underestimates the transvalvular flow, and the greater the regurgitation, the greater the underestimation. This incorrectly small flow determination is then used in the numerator of the Gorlin formula to yield an incorrectly small valve area.

Despite this difficulty, the formula has still proved useful in the evaluation of patients with mixed stenotic and regurgitant lesions. Because the error in flow determination always occurs as an underestimation, one can still calculate a minimum effective valve area, that is, an area indicating the smallest possible orifice size in a given patient, recognizing that the area could be even larger. Even in the setting of regurgitation, if calculated valve area exceeds the critical value, one could eliminate the stenosis as a likely cause of symptoms amenable to surgical correction (whether the regurgitation itself warranted surgical attention became a matter of greater diagnostic concern in the 1960's when valve replacements became available[24,25]).

A final problem in the application of the formula has

centered on mitral valve gradients recorded in patients with aortic regurgitation.[26-29] With the anatomic juxtaposition of aortic outflow tract with mitral leaflets, the regurgitation itself potentially contributed to the mitral valve gradients measured at catheterization. This may represent a functional obstruction to flow. However, in such a situation, the calculated area overemphasizes the severity of a stenotic lesion involving the mitral valve, even creating the appearance of mitral stenosis when it does not exist in some cases.

In an effort to mitigate some of the error-producing factors explored above, the practice of the Yale-New Haven Hospital catheterization laboratory has been to record a given patient's hemodynamic parameters in two physiologic states at the same catheterization - once at rest, and again during an intervention designed to increase flow rates across the valves. The interventions chosen, exercise via supine bicycle ergometry, or catecholamine infusion (isoproterenol or epinephrine) have been shown to increase cardiac outputs and also to influence the extent of backflow in patients with regurgitant lesions, through inotropic, chronotropic, and peripheral vascular effects[24,23,30-47]. It was hoped that these interventions would therefore diminish imprecision generated by spurious variability around small gradients as discussed above, by creating larger gradients with which to calculate areas.

For example as shown previously, in a patient whose resting state MVF was 90 ml/sec, an error of 4 mm Hg in MVG measurement yielded a change in MVA from 2.1 to 1.2 cm^2. A critical value. By stressing the patient and increasing the flow to 291 ml/sec, one now generates a MVG of 20 mm Hg for a valve area of 2.1 cm^2. Under these circumstances, in order to arrive at a miscalculated MVA of 1.2 cm^2, one would have to err greatly in measuring the MVG - by 41 mm Hg instead of a mere 4 mm Hg.

It was felt that errors secondary to the magnitude of a regurgitant fraction could be lessened if the effect of the intervention would be a diminution of the regurgitant fraction of total flow.

With these considerations in mind, I shall review the experience of the Yale-New Haven Hospital catheterization laboratory in order to evaluate the accuracy and usefulness of the Gorlin formula in actual practice, and to assess whether exercise or catecholamine infusion has proven useful in improving the diagnostic precision of this method.

Materials and Methods

Twenty-eight catheterization reports involving 26 adult patients with left-heart valvular lesions were reandomly selected from the period 1971-77 for retrospective analysis. Patients underwent catheterization to document the presence and severity of valvular lesions identified clinically. The general protocol for this procedure involved sedation prior to the performance of right-sided (by vein) and left-sided (by retrograde arterial cannulation) heart catheterization via brachial and/or femoral routes. Pressures were determined by fluid-filled catheters with a frequency response of 25 Hz connected to Statham P23 Db transducers balanced at zero pressure by opening to atmospheric pressure. The zero pressure reference point was taken to be mid-chest. Pressures were then electronically calibrated on an Electronics for Medicine DR-8 recorder (Electronics for Medicine, White Plains, N.Y.) before and after each series of pressure tracings.

Measurement of left atrial pressure was achieved by placement of a catheter in the pulmonary capillary wedge position. For the purpose of determining mitral valve gradients (MVG), pressures from wedge and left ventricular catheters were recorded simultaneously on photographic paper moving at 100 mm/sec. In those patients with aortic stenosis, aortic valve gradients (AVG) were obtained by simultaneous recording of left ventricular and systemic pressures, the latter via a catheter in the central aorta.

Resting cardiac outputs were obtained in the majority of cases via the direct Fick oxygen consumption method, using a three minute air collection period at the same time, or within several minutes of the recording of pressure gradients. According to the Fick equation: Cardiac Output = O_2 consumption divided by arteriovenous oxygen difference. Oxygen consumption was determined by having the patient breathe into a Douglas bag while recording the volume expired during the collection period by a Tissot spirometer. The volume of expired air was corrected to standard dry conditions of pressure and temperature (corrections tables are widely available; for example see reference 48). Oxygen and carbon dioxide content of expired air was analyzed in a device employing the Scholander technique (Otto K. Hebel Scientific Instruments, Rutledge, Pa.)[49] Arteriovenous sampling was at the pulmonary artery and a systemic artery with oxygen content analysis performed on a Lex-O_2-Con oxygen analyzer (Lexington Instruments Corp., Waltham, Mass.) During the intervention state (either exercise or catecholamine infusion), the air collection period varied from one to three minutes, during a time when hemodynamic state had stabilized. In a few cases, outputs were measured by the indocyanine green dilution method.[22]

Six patients bicycled in the supine position, during which time pressure and output studies were completed. Patients with aortic stenosis were not considered candidates for this maneuver. Ten patients were infused intravenously with an

epinephrine drip at a rate of two to four mcg/min. Similarly, twelve patients a two to four mcg/min infusion of isoproterenol.

Following an intervention, left ventriculograms, aortograms, and coronary arteriography (in most patients) were performed using standard techniques and were recorded on 35 mm ciné film. Valvular regurgitation was assessed according to the criteria of Sellers, et al: 1+ indicated a puff of injected radio-opaque contrast material traversed a valve during its closure period, with rapid clearing of the contrast material subsequetnly; 2+ indicated faint opacification of the entire chamber proximal to the valve (atrium or ventricle) with rapid clearing; 3+ indicated opacification of equal degree on both sides of the valve, occurring immediately after injection; and 4+ indicated greater opacification proximal to the valve than distal.[50] Regurgitation of 1+ was considered insignificant, and for the purpose of this study patients with 1+ regurgitation and stenosis were grouped with those with pure stenosis. Throughout the cath procedure, patients were monitored with a Lead II electrocardiogram, recorded simultaneously with the pressure tracings.

Valve areas were computed by the Gorlin formula (see Figure 3). Heart rate was determined from the electrocardiogram over five or ten cycles depending on the regularity of the rhythm (five for sinus rhythm). Diastolic filling period was measured as the time between the points of inter-

section of the pulmonary capillary wedge tracing (PCW) with the upstroke and downstroke of the left ventricular pressure curve. Similarly, the systolic ejection period (sec/beat) was determined by measuring the time distance between the intersection of the systemic pressure curve with the simultaneously plotted left ventricular pressure curve.

Pressure gradients were calculated by hand digitization over 40 millisecond intervals (time lines provided by the photographic recorder) and at pressure sensitivities of 0 to 40 mm Hg for the mitral valve and 0 to 200 mm Hg for the aortic valve. Mean pressures were obtained by electronic damping of the pressure signals. Gradients, heart rates, and flow periods were averaged over five cardiac cycles for patients in sinus rhythm, or over 10 cycles in patients with atrial fibrillation or sinus rhythm with ectopy. Extraction of data from pressure tracings was performed by members of the Section of Cardiology at the time of catheterization. For the purposes of this study, I reviewed all data for accuracy and recalculated information as indicated.

Mean systemic pressure in mm Hg, right atrial pressure in mm Hg, and cardiac output were utilized to compute total systemic vascular resistance (TSVR): TSVR in

$$\text{dynes}\cdot\text{sec}\cdot\text{cm}^{-5} = \frac{\text{systemic - right atrial pressure}}{\text{cardiac output (l/min)}} \times 80 \quad (51)$$

Prior to angiography, left ventricular end-diastolic pressure (LVEDP) was measured at high sensitivity (0 to 40 mm Hg scale) and recorded as the pressure at the end of the left ventricular

$$\text{VALVE AREA} = \frac{\text{Transvalvular Flow}}{C \times 44.5\sqrt{\text{Pressure Gradient}}}$$

Mitral valve flow (MVF) = Cardiac Output (ml/min)/Diastolic Filling Period

Diastolic Filling Period = diastolic filling period (sec/beat) x HR

HR = heart rate (beats/min)

Aortic valve flow (AVF) = Cardiac Output (ml/min)/SEP

Systolic Ejection Period (SEP) = systolic ejection period (sec/beat) x HR

For the mitral valve, C = 0.7. For the aortic valve, C = 1.0.

Figure 3

a wave, or when the a wave was not present, as the pressure forty milliseconds after the onset of the QRS complex on the electrocardiogram.

Patients have been grouped into six categories: pure mitral stenosis; pure aortic stenosis with or without associated mitral stenosis; mitral stenosis, including those with associated aortic stenosis; mitral stenosis and mitral regurgitation; mitral stenosis with aortic regurgitation; mitral stenosis with aortic or mitral regurgitation. The magnitude of change of valvular areas measured in two different states has been defined as the difference between resting and intervention valve areas divided by resting valve areas. Statistical analysis of data has been performed using paired two-tailed t-tests. Results have been considered significant for a level of probability (p) less than 0.05. Values are expressed ± the standard deviation.[52]

Results

Mitral Stenosis

Table I presents the data available on sixteen patients whose catheterization studies documented mitral stenosis (MS) as the predominant left-sided lesion. One patient (WE) had severe tricuspid regurgitation but was included because right-sided regurgitation did not interfere with the mitral valve flow determination. Patients ranged in age from 21 to 64, and all were female. Because of the small number of patients involved, resting state values were compared to intervention state values, without differentiation between catecholamine infusion or exercise for the purpose of the paired t-test analysis.

Mean cardiac outputs increased from 4.1±2.0 to 6.6±3.8 l/min ($p=3.4\times10^{-3}$) from resting to intervention state. In the twelve patients evaluated, oxygen consumption increased from 158±34 to 260±156 ml/min ($p=3.8\times10^{-2}$). Heart rate rose from 81±14 to 128±28 beats/min ($p=3.0\times10^{-6}$). Data needed to calculate TSVR were available in only three patients, all of whom received isoproterenol. In all cases, TSVR declined with the infusion. The diastolic filling period remained essentially stable, but the mitral valve flow rose from 151±89 to 233±124 ml/sec ($p=1.4\times10^{-3}$). Pulmonary capillary wedge pressures changed from 14±5 to 25±9 mm Hg ($p=3.8\times10^{-6}$), and the MVG approximately doubled, 8.1±3.3 to 16.6±5.7 mm Hg ($p=1.4\times10^{-6}$). Left ventricular end-diastolic pressures were unchanged.

Mitral valve areas calculated at rest ranged from 0.5 cm^2 to 5.1 cm^2 (mean 1.8±1.1 cm^2). Intervention MVAs ranged from 0.5 to 4.4 cm^2 (mean 2.0±1.1 cm^2). Resting and intervention valve areas did not differ significantly by paired analysis. The magnitude of change ranged from 0 to 0.57. Four patients had no change in MVA. In six, valve areas rose (increments of 0.2 to 1.6 cm^2), and in five, valve areas declined (decrements 0.1 to 0.8 cm^2). Of the eleven pairs of MVAs exhibiting a change, areas varied by 0.2 cm^2 or less in five.

MVAs changed from critical to non-critical values in only one case (KJ). Despited this cross-over, this patient underwent operation, for unclear reasons. At operation, her lesion was simply described as "tight." In addition, patient MB underwent closed mitral commisurotomy, althuugh both calculated MVAs were non-critical values. Favoring an operative approach despite these data was this patient's recurrent episodes of pulmonary edema. The surgeons found a slightly stenotic valve not admitting the tip of the index finger, to paraphrase their report.

Altogether, three patients underwent closed mitral commisurotomy, one patient had an open mitral commisurotomy, and one patient had placement of prosthetic mitral and tricuspid valves. In their operative reports, surgeons only roughly assessed the degree of stenosis, describing valve areas in terms of fingertips or in one case, in terms of centimeters

of diameter. These crude but direct assessments did not permit a precise appraisal of the accuracy of the catheterization determined areas, although stenosis was found in each case.

Aortic Stenosis

Table II concerns three patients with aortic stenosis, one of whom had concomitant mitral stenosis (JC) and was studied on two separate occasions. At the time of catheterization, patients' ages ranged from 45 to 64 years. All were male.

Mean cardiac output climbed from 6.0±1.9 to 9.9±4.5 l/min with interventions (consisting of epinephrine infusion in three instances, and isoproterenol in one). As in the isolated MS group, certain parameters increased: oxygen consumption from 350±161 to 377±113 ml/min, heart rate from 66±8 to 85±8 beats/min, valve flow, from 310±118 to 464±217 ml/sec, PCW, from 18±2 to 26±2 mm Hg, aortic valve gradient, from 24±11 to 39±19 mm Hg. Except for PCW ($p=0.02$), these increases did not achieve statistical significance, given the small numbers of patients studied.

Systolic ejection period rose slightly, from 19.6±1.1 to 21.6±3.4 sec/min, left ventricular systolic pressure increased from 155±22 to 196±26 mm Hg, but mean systemic pressure appeared stable. Left ventricular end-diastolic pressures also increased slightly in most patients (from 19±6 to 25±11 mm Hg).

Changes in hemodynamic parameters were of a magnitude sufficient to achieve statistical significance in only two other areas - TSVR and AVA. Total systemic vascular resistance declined from 1150±381 to 802±404 dynes·sec·cm^{-5} ($p=1.7\times10^{-3}$). Aortic valve area increased in every patient (increments from 0.1 to 0.3 cm^2, giving a magnitude of change ranging from 0.07 to 0.25). Mean AVAs were 1.6±0.9 cm^2 at rest and 1.8±0.9 cm^2 during intervention ($p=1.6\times10^{-2}$). Separating patients with isolated (pure) aortic stenosis (patients LP and RD) from the others, one sees the same kinds of changes evident in the mean data as in the whole group (bottom, Table IIA). All calculated AVAs represented non-critical values.

Two patients subsequently underwent cardiac surgery, one receiving a coronary artery bypass graft and an aortic valve replacement, the other, aortic and mitral valve replacements. The latter patient had concomitant MS with a critical resting MVA of 1.2 cm^2. Operative findings were not phrased in such a way as to permit appraisal of the precise accuracy of the valve area calculations, but no gross discordance became manifest. Of importance is that in three instances of increased AVA, no regurgitation was demonstrated angiographically. Therefore, flow error secondary to regurgitation was unlikely to have contributed to the valve area increases.

As indicated in Table IIB. one patient with AS was studied twice and shown to have mitral stenosis, with MVA of 1.6 cm^2

falling to 1.4 cm^2 with epinephrine infusion (first catheterization), and 1.2 cm^2 rising to 1.6 cm^2 (second cath), giving a magnitude of change of 0.13 and 0.33 respectively. Pertinent data have been included with values from Table IA, patients with isolated MS, and analyzed (Table III). Changes of a direction similar to those of Table IA were evident, with the persistent result that MVAs did not change from resting to intervention states in a statistically significant way. However, the addition of an extra pair of values for TSVR accorded significance ($p=0.04$) to the group decline of 1840 ±882 to 1443±868 dynes.sec.cm-5.

Mitral Stenosis and Regurgitation

Table IV consists of data collected from three patients with MS and concomitant 2 to 3+ mitral regurgitation (MR). Two females and one male comprised the study group, with ages ranging from 29 to 55 years. Sample size was too small for statistical significance to be demonstrated, but mean cardiac output (4.2±1.4 to 8.3±5.0 l/min), oxygen consumption (218±35 to 581±433 ml/min), DFP (30.4±1.2 to 35.2±8.2 sec/min), MVF (138±50 to 284±251 ml/sec), PCW (13±5 to 18±8 mm Hg), MVG (6.6±2.7 to 14.8±8.6 mm Hg), and heart rate (74±10 to 91±22 beats/min) all increased. Left ventricular end-diastolic pressure declined slightly (11±8 to 7±3 mm Hg). Mean MVA (1.9±0.9 cm^2) rose with the interventions (to 2.2±1.3 cm^2). Two of three valve areas exhibited a rise (magnitude of change

0.31 and 0.12), with the remaining area holding constant. No cross-overs from critical to non-critical areas occurred on repeat measurement.

Two patients underwent operative treatment, one receiving a mitral valve replacement, the other mitral and aortic valve replacements. Apparent discrepancies between pre-operative assessments of the cardiac lesions and operative findings were identified in both cases. AS was noted to have severe aortic regurgitation while on heart-lung bypass, although angiography had indicated only trivial aortic regurgitation. SG had calculated MVAs and a cardiac echo indicative of only moderate mitral stenosis; yet the surgeons reported that a stenotic valve with a 1 cm diameter (yielding an area of approximately 0.8 cm^2 if one assumes area = $(\pi)(radius)^2$) was present on direct inspection.

Mitral Stenosis and Aortic Regurgitation

Table VA presents the data collected on five patients (four females, one male) with catheterization findings consistent with mitral stenosis and aortic regurgitation. One patient had aortic stenosis as well (VH). Ages of these subjects ranged from 27 to 65. All patients received catecholamine infusions during intervention measurements (four had isoproterenol, one had epinephrine). As in other patient groups, cardiac outputs, heart rates, mitral valve flows, systolic pressures, and mean systemic pressures all increased with

intervention (3.4±1.1 to 8.8±7.0 l/min, 79±13 to 126±26 beats/min, 108±38 to 275±179 ml/sec, 142±17 to 153±40 mm Hg, and 78±18 to 92±22 mm Hg respectively). Changes were statistically significant for heart rate only. In addition, total systemic vascular resistance, oxygen consumption (data available in only two patients), and left ventricular end-diastolic pressures declined (1977±544 to 1023±826 dynes.sec.cm^{-5}, 185±115 to 142±38 ml/min, 13±6 to 5±3 mm Hg respectively). Changes were statistically significant for TSVR ($p=0.047$) and LVEDP ($p=0.019$). Diastolic filling periods and pulmonary capillary wedge pressures remained stable (32.5±7.2 sec/min to 31.7±4.0 sec/min and 17±8 to 15±5 mm Hg respectively).

Resting MVA ranged from 0.6 to 2.3 cm^2, averaging 1.4±0.7 cm^2. With intervention, mean MVA rose to 3.2±3.5 cm^2 (range of individual values 0.9 to 9.4 cm^2). These changes represented magnitudes of change ranging from 0 to 14.6. However, the increase in mean MVA was not statistically significant. Valve areas crossed from critical to non-critical values in two patients (HE and SP), and remained stable in two. One patient whose valve area crossed over did not undergo subsequent operation (SP), while HE received surgical therapy to correct his severe aortic regurgitation. At operation, his mitral valve was normal, despite the preoperative calculated MVA of 0.6 cm^2 at rest.

Two other patients received surgical relief. DM underwent closed mitral commisurotomy; a stenotic valve was noted

on direct examination. Patient VH underwent aortic valve replacement of her critically stenotic aortic valve. Her angiographically moderately severe aortic regurgitation was verified at operation. However, despite calculated MVAs at rest and intervention consistent with moderate mitral stenosis, surgeons found no mitral lesion.

Mitral Stenosis and Left-sided Regurgitation

Table VI presents an analysis of all seven pairs of rest-intervention MVAs in patients with associated aortic and/or mitral regurgitation. Although mean valve area increased (1.6 ± 0.8 to 2.8 ± 2.8 cm^2), the difference was not statistically significant.

TABLE IA - MITRAL STENOSIS

PT	CO	$\dot{V}O_2$	HR	TSVR	DFP	MVF	PCW	MVG	LVSP/DP-EDP	SP (MEAN)	MVA
GC	4.1 (R)	141	71	1706	32.6	138	10	4	140/0 - 8	135/70 (100)	2.2
	10.6 (Ep)	233	121	NA	30.2	351	18	15	NA/0 - 2	NA	2.9
AL	3.2 (R)	138	90	2370	23.4	137	22	6	145/0 - 13	145/80 (100)	1.8
	4.5 (Ep)	161	160	NA	21.8	209	24	14	NA/0 - 15	NA	1.8
KJ	3.1 (R)	212	100	2500	28.8	108	18	12	140/0 - 8	140/80 (100)	1.0
	6.3 (Ep)	259	120	NA	31.6	199	24	16	NA/0 - 8	NA	1.6
JC	3.2 (R)	177	60	1850	36.0	89	18	7.5	100/0 - 12	95/60 (80)	1.0
	4.7 (Ep)	263	95	NA	34.0	138	36	21	NA/0 - 9	NA	1.0
WE	3.1 (R)	109	60	2110	35.2	88	22	14	120/0 - 20	110/58 (90)	0.8
	3.8 (Ep)	167	76	NA	36.3	105	39	20	NA - 29	NA	0.8
BJ	2.4 (R)	151	75	2700	16.5	146	11	3.8	120/0 - 10	120/60 (90)	2.4
	1.9 (Is)	139	154	NA	14.0	136	12	3.9	140/0 - 8	NA	2.2
DL	3.4 (R)	158	64	2100	26.9	126	7	3.8	140/0 - 4	140/60 (90)	2.1
	3.8 (Is)	182	140	1980	27.6	138	12	9	160/0 - 2	160/60 (98)	1.5
AS	3.4 (R)	195	76	2450	37.7	90	16	9	140/0 - 8	144/70 (110)	1.0
	5.7 (Is)	247	180	NA	29.5	193	27	25	NA	NA	1.2
DL	7.0 (R)	445	110	920	30.8	227	17	12	90/5 - 10	90/65 (80)	2.1
	9.0 (Is)	NA	140	NA	28.0	321	26	18	NA	NA	2.4
PO	3.45 (R)	202	78	2900	31.2	111	16	7.5	190/4 - 13	190/90 (130)	1.3
	4.83 (Is)	287	95	2250	27.6	175	36	14.3	200/20 - 30	200/100 (140)	1.5
JS	5.2 (R)	121	71	811	33.7	220	8	6.4	100/0 - 4	95/75 (80)	2.8
	16.3 (Is)	220	99	313	32.5	511	16	13.7	115/0 - 4	100/60 (70)	4.4
VK	1.9 (R)	123	83	3632	35.7	53.2	18	10	120/0 - 2	120/80 (95)	0.5
	2.1 (Ex)	229	125	NA	27.5	76.4	35	24	115/0 - 5	NA	0.5

TABLE IA - MITRAL STENOSIS (CONTINUED)

PT	CO	$\dot{V}O_2$	HR	TSVR	DFP	MVF	PCW	MVG	LVSP/DP-EDP	SP (MEAN)	MVA
AG	4.2 (R)	NA	87	1800	26.6	158	18	11.5	142/0 - 12	147/80 (100)	1.5
	6.2(Ex)	NA	160	NA	32.1	193	35	23	NA	NA	1.3
JS	10.3 (R)	NA	111	730	23.5	438	11	7.5	127/1 - 6	127/85 (99)	5.1
	11.5 (Ex)	NA	135	NA	25.7	447	16	11	120/0 - 1	NA	4.3
MB	3.9 (R)	156	97	1436	25.5	147	12	10	90/0 - 2	80/60 (70)	1.5
	5.7 (Ex)	NA	125	NA	28.9	198	28	21	NA/0 - 5	NA	1.4
LH	4.0 (R)	168	84	1780	28.8	139	7	5	100/0 - 7	100/72 (85)	2.0
	8.8 (Ex)	734	125	NA	26.4	332	20	17	NA/0 - 12	NA	2.6
						MEAN VALUES*					
REST	4.1±2.0	158 ±34	81 ±14	1937 ±1054	29.5 ±5.7	151 ±89	14 ±5	8.1 ±3.3	133±31[a] - 9±5[b]	100±26[c]	1.8 ±1.1
INT	6.6±3.8	260 ±156	128 ±28	1514 ±1049	28.4 ±5.2	233 ±124	25 ±9	16.6 ±5.7	142±34 - 10±10	103±35	2.0 ±1.1
TOTAL PAIRS	16	12	15	3	16	16	15	16	6[a] - 13[b]	3	16
p	3.4 x10-3	3.8 x10-8	3.0 x10-6	NS	NS	1.4 x10-3	3.8 x10-6	1.4 x10-6	NS - NS	NS	NS

TABLE IB - MITRAL STENOSIS

PT

GC 46 y.o. F. Hx RF, age 11. S/P two previous mitral commisurotomies (last, five years prior to this cath). Sx: exertional chest pain, dyspnea on exertion. EKG - NSR. Angio: no regurgitation, significant CAD. No operation subsequent to cath as of 5/77 (1.7 yrs. post cath).

AL 64 y.o. F. S/P mit. commis. (11 yrs. prior to this cath). Sx: increasing fatigue, dyspnea, chest heaviness. EKG - AF. Angio: 1+ MR; no CAD. No subsequent operation known.

KJ 46 y.o F. Sx: PND x 1. EKG - AF. Angio: stiff, domed mitral valve; 1+ AR; no CAD. Op: open valvulotomy revealing "tight" stenosis. Pressure tracings from cath not available for review.

JC 37 y.o F. Hx RF. Sx: increasing dyspnea. EKG - NSR. Angio: no regurg.; no CAD. Op: closed mitral commisurotomy; valve diameter estimated at 1 cm.

WE 61 y.o. F , carrying dx RHD. S/P mitral commisurotomy, twenty yrs. previous to cath. Sx: increasing fatigue, dyspnea on exertion. EKG - AF. Angio: trace MR, 1+ AR, 4+ TR; no sig. CAD. Op: MVR, TVR with porcine heterografts; valve lesions not described in op note.
S/P closed mit. commis. (3 yrs. prior to cath.)

BJ 59 y.o. F. Hx RF.^ Sx: increasing dyspnea. Previous episodes of pulmonary edema; questionable hx of MI. EKG - AF. Angio: dyskinetic apex; 1+ AR; no CAD. No subsequent operation known (as of 3 yrs post cath).

DL 62 y.o. F. Sx: dyspnea on exertion, orthopnea. EKG - NSR. Angio: trace AR; minor CAD. No subsequent opration known.

AS 43 y.o. F, carrying dx RHD. S/P mit. commis. 6mos. prior to cath. Sx: persistent dyspnea on exertion and fatigue. Angio: trace AR; no CAD. No subsequent op known.

DL 50 y.o. F. Questionable hx RF. S/P mit. commis. 15 yrs. prior to cath. Sx: increasing fatigue, dyspnea on exertion. EKG - AF. Angio: no regurg. or CAD. No subsequent op known.

PO 57 y.o. F. Hx RF, S/P mit. commis 10 yrs. prior to cath. Sx: dyspnea on exertion, chest pain. EKG - AF. Angio: severe CAD; no regurg. No known op as of 8 mos. post cath.

JS 34 y.o. F. Hx RF. Sx: increasing fatigue, dyspnea on exertion, orthopnea, hemoptysis. Hx of pulmonary embolism in past. EKG - NSR. Angio: minimal MR occurring during extra-systoles, 1+ AR; no CAD. No known op subsequent to cath.

TABLE IB - MITRAL STENOSIS (CONTINUED)

PT

VK 34 y.o. Sx: decreased exercise tolerance, dyspnea on exertion. EKG - NSR. Angio: 1+ AR; no CAD. Op: closed mitral commisurotomy; valve admitted a fingertip.

AG 58 y.o. F. Sx: mild fatigue. Hx CHF responsive to medical therapy; hematuria (? stones). Referred for cath because of increasing liver size and right atrial size (on CXR) to evaluate possible right ventricular failure. EKG - AF. Angio: not performed. No known op as of 3 yrs. post cath.

JS 27 y.o. F. Hx RF. Sx: near-syncope, palpitations. EKG - NSR. Angio: minimal MR and AR; no CAD. No op recorded as of 6 yrs. post cath.

MB 21 y.o. F. Sx: mild dyspnea on exertion and chest pain; hx of pulmonary edema x 4 EKG - NSR. Angio: no regurg; no CAD. Op: closed mitral commisurotomy revealing slightly stenotic valve not admitting tip of index finger.

LH 28 y.o. F. Sx: dyspnea on exertion. Hx of pulmonary edema x 1. EKG - NSR alternating with low atrial rhythm. Angio: no regurg.; no CAD. No subsequent op known as of 1.5 yrs. post cath.

PT	CO	VO_2	HR	TSVR	SEP	AVF	PCW	AVG	LVSP/DP-EDP	SP (MEAN)	AVA
LP	8.7 (R)	589	65	791	18.0	483	16	15	140/4 - 16	125/60 (96)	2.8
	16.4 (Ep)	543	95	428	20.8	790	24	35	220/6 - 34	170/75 (100)	3.0
RD	5.5 (R)	276	77	1110	19.5	284	18	23.5	145/0 - 12	135/80 (85)	1.3
	8.8 (Ep)	343	83	747	24.9	353	28	31.3	168/0 - 10	138/75 (90)	1.4
JC	5.1 (R)	292	64	1550	20.7	246	20	18	180/0 - 24	160/80 (107)	1.3
	6.0 (Ep)	331	75	1230	17.2	349	26	24	200/0 - 30	160/70 (100)	1.6
JC	4.5 (R)	241	58	1636	20.0	225	24	40	180/0 - 22	150/63 (96)	0.8
	8.5 (Is)	291	86	NA	23.3	364	NA	67	NA - 24	NA	1.0
						MEAN VALUES					
REST	6.0 ±1.9	350 ±161	66 ±8	1150 ±381	19.6 ±1.1	310 ±118	18 ±2	24 ±11	155±22 - 19±6	96±11	1.6 ±0.9
INT	9.9 ±4.5	377 ±113	85 ±8	802 ±404	21.6 ±3.4	464 ±217	26 ±2	39 ±19	196±26 - 25±11	97±6	1.8 ±0.9
TOTAL PAIRS	4	4	4	3	4	4	3	4	3 - 4	3	4
p	NS	NS	NS	1.7 x10-3	NS	NS	0.02	NS	NS - NS	NS	1.6 x10-2
						PURE AORTIC STENOSIS					
REST	7.1 ±2.2	433 ±221	71 ±9	951 ±226	18.8 ±1.1	384 ±141	17 ±1	19 ±6	143±4 - 14±3	91±8	2.1 ±1.1
INT	12.6 ±5.4	443 ±141	89 ±9	586 ±226	22.9 ±2.9	572 ±309	26 ±3	33 ±3	194±37 - 22±17	95±7	2.2 ±1.1
TOTAL PAIRS	2	2	2	2	2	2	2 (ALL NS)	2	2 - 2	2	2

TABLE IIB - AORTIC STENOSIS

PT

LP 64 y.o F. Sx: increasing dyspnea, exertional chest pain. Hx of COPD. EKG - NSR. Angio: no regurg; moderate CAD; small left ventricular cavity with septal and papillary muscle hypertrophy. No subsequent op as of 4.5 yrs post cath.

RD 55 y.o. M. Sx: chest pain, dyspnea on exertion. Hx hypertension. EKG - NSR. Angio: no regurg; increased left ventricular size with normal ejection fraction; inferior wall akinesis; proximal right CAD and minimal left CAD. Op: CABG and AVR, revealing calcified, bicuspid aortic valve.

JC 54 y.o. M. Hx RF. Sx: dizziness, headaches. EKG - NSR. Additional cath data: REST - MVG 12.4, DFP 29.0, MVF 176, MVA 1.6. INT - MVG 16.8, DFP 33.6, MVF 179, MVA 1.4. Angio: no regurg; no CAD; ? cardiomyopathy.

JC 55 y.o. M (same pt. as above, 1.8 yrs. later). Sx: dyspnea, fatigue, recent episode of pulmonary edema, complicated by onset of rapid AF. EKG - sinus rhythm. Additional cath data: REST - MVG 8, DFP 42.6, MVF 106, MVA 1.2. INT - MVG 17, DFP 41.4, MVF 205, MVA 1.6. Angio: left ventricular hypertrophy, left atrial enlargement, trace pre-systolic mitral regurgitation and 1+ systolic mitral regurgitation, probable Type III aortic dissection. Op: AVR and MVR, revealing calcified valves. Valve diameters not described; ? old, calcified aortic dissection.

BOTH ISOLATED AND WITH AORTIC STENOSIS

MEAN VALUES

	CO	$\dot{V}O_2$	HR	TSVR	DFP	MVF	PCW	MVG	LVSP - EDP	MEAN SP	MVA
REST	4.2 ±1.9	173 ±51	80 ±17	1840 ±882	30.3 ±6.2	150 ±84	15 ±5	8.4 ±3.2	140±33 - 10±7	102±22	1.7 ±1.1
INT	6.7 ±3.6	267 ±145	123 ±30	1443 ±868	29.4 ±5.9	228 ±118	25 ±9	16.7 ±5.4	150±38 - 12±11	102±29	1.9 ±1.1
TOTAL PAIRS	18	14	18	4	18	18	17	18	7 - 15	4	18
p	1.3 x10-3	2.6 x10-2	2.9 x10-6	0.04	NS	7.3 x10-4	2.3 x10-6	2.2 x10-7	NS - NS	NS	NS

PT	CO	$\dot{V}O_2$	HR	TSVR	DFP	MVF	PCW	MVG	LVSP/DP-EDP	SP (MEAN)	MVA	MR
SG	5.7 (R)	243	79	1404	29.2	195	8	5	170/0 - 6	150/89 (105)	2.8	2+
	14.1 (Ex)	887	86	NA	27.4	514	25	21	NA/0 - 10	NA	3.6	
AS	3.1 (R)	193	80	2348	30.4	102	12	9.7	140/0 - 6	140/70 (93)	1.1	2+
	5.1 (Ep)	275	115	NA	34.5	148	20	18.5	180/0 - 4	180/60 (100)	1.1	
JS	3.7 (R)	151	62	2400	31.6	117	18	5	150/5 - 20	150/80 (103)	1.7	2-3+
	5.7 (Is)	NA	71	870	43.8	130	10	5	150/0 - 7	110/40 (70)	1.9	
						MEAN VALUES						
REST	4.2 ±1.4	218 ±35	74 ±10		30.4 ±1.2	138 ±50	13 ±5	6.6 ±2.7	145±7 - 11±8	98±7	1.9 ±0.9	
INT	8.3 ±5	581 ±433	91 ±22		35.2 ±8.2	284 ±251	18 ±8	14.8 ±8.6	165±21 - 7±3	85±21	2.2 ±1.3	
TOTAL PAIRS	3	2	3		3	3	3	3	2 - 3	2	3	
p	NS	NS	NS		NS	NS	NS	NS	NS - NS	NS	NS	

TABLE IVB - MITRAL STENOSIS AND REGURGITATION

PT

orthopnea, palpitations,

SG 29 y.o. F. Sx: dyspnea on exertion, decreased exercise tolerance. EKG - NSR. Cardiac echo: E-F slope 22mm/sec (consistent with moderate stenosis); ejection fraction 80%. Angio: ejection fraction 40%, although technical adequacy of estimation questionable; 2+ MR; 1+ AR; aortic leaflets appeared thickened and domed. Op: MVR, revealing "about a 1 cm orifice" and minimal to moderate mitral regurgitation. Presence of calcium not described at angio or at op.

AS 55 y.o. M. Hx RF. Sx: orthopnea, PND, ankle edema. Hx cerebral embolism in past. EKG - sinus rhythm. Angio: 2+ MR; 1+ AR; prominent papillary muscles; normal ejection fraction; no CAD. Op: AVR and MVR, revealing a large heart with 2500 ml/min estimated aortic regurg. while on heart-lung bypass. Valves not described.

JS 32 y.o. F. Hx RF; S/P mitral commis. 8 yrs prior to cath. Sx: increasing fatigue, dyspnea on exertion. EKG - sinus rhythm. Angio: moderate MR, minimal AR; no CAD. No subsequent op as of 5 yrs. post cath.

TABLE VA - MITRAL STENOSIS AND AORTIC REGURGITATION

PT	CO	$\dot{V}O_2$	HR	TSVR	DFP	MVF	PCW	MVG	LVSP/DP-EDP	SP (MEAN)	MVA	AR
HE	2.6 (R)	210	75	1600	43.0	60.7	31	12	130/7 - 20	130/50 (60)	0.6	4+
	21.1 (Is)	NA	90	220	36.0	586	10	4	130/0 - 6	128/41 (67)	9.4	
DM	2.7 (R)	103	60	2900	32.1	84.1	16	9	150/0 - 16	140/60 (90)	0.9	2+
	4.2 (Is)	115	150	NA	36.0	151	22	29	NA/0 - 4	NA	0.9	
SP	3.6 (R)	185	85	1730	32.8	110	14	11	135/0 - 9	125/60 (80)	1.2	2+
	7.6 (Is)	NA	150	979	29.5	258	14	17	130/0 - 6	130/70 (98)	2.0	
SG	5.1 (R)	260	96	1640	31.8	160	8	5.0	146/0 - 4	146/80 (110)	2.3	2+
	6.5 (Is)	NA	128	NA	29.8	218	12	9.3	NA/0 - 0	NA	2.3	
VH	2.8 (R)	266	78	2600	22.6	124	16	5	162/0 - 16	154/70 (95)	1.8	3+
	4.5 (Ep)	169	113	1870	27.4	164	18	13	200/0 - 8	165/80 (110)	1.5	
MEAN VALUES												
REST	3.4 ±1.1	185 ±115	79 ±13	1977 ±544	32.5 ±7.2	108 ±38	17 ±8	8.4 ±3.3	142±17 - 13±6	78±18	1.4 ±0.7	
INT	8.8 ±7.0	142 ±38	126 ±26	1023 ±826	31.7 ±4.0	275 ±179	15 ±5	14.5 ±9.4	153±40 - 5±3	92±22	3.2 ±3.5	
TOTAL PAIRS	5	2	5	3	5	5	5	5	3	5	3	5
p	NS	NS	2.4 x10-2	4.7 x10-2	NS	NS	NS	NS	NS	0.019	NS	NS

TABLE VB - MITRAL STENOSIS AND AORTIC REGURGITATION

PT

HE 65 y.o. M. Sx: dyspnea on exertion and at rest. Hx includes past episodes of embolization to ilio-femoral vessels. EKG - AF. Angio: enlarged left ventricular cavity; stiff appearing mitral valve; 1+ MR; 4+ AR; no CAD. Op; AVR for AR; mitral valve not described.

DM 49 y.o. F. Hx RF. Sx: dyspnea, fatigue, palpitations. EKG - AF. Angio: trace MR; 2+ AR; no CAD. Op: closed mitral commisurotomy, revealing a mitral valve orifice barely admitting a finger; AR not assessed.

SP 49 y.o. F. Hx RF. Sx: increasing dyspnea on exertion, orthopnea. Carries dx of progressive systemic sclerosis. EKG - sinus rhythm. Angio: 1+MR; 2+AR; no CAD. Ectopy present during resting pressure measurement.

SG 27 y.o. F. Sx: increasing dyspnea, occasional ankle edema. EKG - sinus rhythm at rest; AF during isoproterenol infusion. Angio: mild to moderate AR. Pt. re-cath'ed two yrs. later and found to have 2+MR and 1+ AR (see Table IV). Earlier angio film not available for review.

VH 51 y.o. F. Hx RF. Sx: progressive fatigue, dyspnea on exertion, intermittent pressing retrosternal pain. EKG - sinus rhythm. Additional cath data: REST - AVG 20, SEP 23.6 AVF 119, AVA 0.5 INT - AVG 52, SEP 25.8, AVF 174, AVA 0.5. Angio: ejection fraction normal; 2+ MR; 2-3+ AR; decreased mitral valve mobility; 1-2+ left ventricular hypertrophy; doming, tricuspid aortic valve; no CAD. Op: AVR revealing a stenotic aortic valve but no mitral lesion; AR estimated at 2 l/min during fibrillation.

TABLE VI - COMBINED MITRAL STENOSIS AND AORTIC OR MITRAL REGURGITATION. GROUP COMPARISON.

	MVA
REST	1.6±0.8
INT	2.8±2.8
TOTAL PAIRS	7
p	NS

Legend for Tables I through VI

Abbreviations: PT-patient; CO-cardiac output (liters/minute); $\dot{V}O_2$-oxygen consumption (milliliters/minute); HR-heart rate (beats/minute); TSVR-total systemic vascular resistance (dynes·sec·cm^{-5}); DFP-diastolic filling period (seconds/minute); MVF-mitral valve flow (milliliters/sec); AVF-aortic valve flow (milliliters/sec); PCW-pulmonary capillary wedge pressure (mm Hg); MVG-mitral valve gradient (mm Hg); AVG-aortic valve gradient (mm Hg); LVSP-left ventricular systolic pressure (mm Hg); DP-diastolic pressure (mm Hg); EDP-left ventricular end-diastolic pressure (mm Hg); SP (MEAN)-systemic pressure (mm Hg); SEP-systolic ejection period (sec/minute); MVA-mitral valve area (cm^2); AVA-aortic valve area (cm^2); R-resting state; Ex-exercise state; Is-isoproterenol infusion state; Ep-epinephrine infusion state; y.o.-year-old; F-female; M-male; Hx-history; RF-rheumatic fever; S/P-status post; Sx-symptoms; Angio-angiography; EKG-electrocardiogram; NSR-sinus rhythm; AR-aortic regurgitation; MR-mitral regurgitation; CAD-coronary artery disease; dx-diagnosis; AF-atrial fibrillation; RHD-rheumatic heart disease; Op-operation; PND-paroxysmal nocturnal dyspnea; MVR-mitral valve replacement; AVR-aortic valve replacement; TVR-tricuspic valve replacement; CHF-congestive heart failure; NA-not available.

* Mean values were computed using data from patients in whom both resting (REST)and intervention (INT) studies were undertaken, since only paired values could be incorporated into the t-test. Hence, in Table IA, all 16 patients had both resting and intervention cardiac outputs measured, and so means were based on data from all 16 patients (as indicated in the row marked Total Pairs). However, for the category $\dot{V}O_2$, complete data were available from both states in only 12 patients, and so only 12 pairs were used to calculate the means. P refers to statistical probability. NS indicates results were not statistically significant.

a Value shown represents LVSP.

b Value shown represents LVEDP.

c Value shown represents mean SP.

Discussion

The present investigation has focused on the utility of the Gorlin formula in assessing the severity of valvular heart disease and the desirability of operative correction. Specifically looked at was the usefulness of repeating measurements after inducing hemodynamic stress in a given patient, either by infusing a catecholamine or having the patient exercise in the supine position.

The interventions produced hemodynamic changes similar to those reported by others[21,23,30-47]. In all patient categories, mean cardiac output, heart rate, transvalvular gradients, and oxygen consumption (except in the Mitral Stenosis/Aortic Regurgitation group, where oxygen consumption was available in only two subjects) increased. Mean pulmonary capillary wedge pressures rose consistently in all except those with significant aortic regurgitation. Total systemic vascular resistance declined, consistent with the vasodilatory effect of the catecholamines employed in the small number of patients for whom data were available. Data were highly variable with respect to DFP and SEP, left ventricular systolic pressures, and left ventricular end-diastolic pressures.

In the Mitral Stenosis group, valve areas varied in individual patients, but in 16 of 18 patients did not change from a critical to non-critical value. By statistical analysis, intervention areas did not differ significantly from resting values. This result confirms the consistency of the

Gorlin formula when applied to patients with pure mitral stenosis in a variety of hemodynamic settings. In this study, repetition of hemodynamic measurements during an intervention state has not proven useful.

In contrast to the Mitral Stenosis group, patients with aortic stenosis showed a small increase (0.2 cm^2) in calculated AVA when hemodynamically stressed by catecholamine infusion. This interesting finding has been demonstrated in two other studies, both involving exercise as the intervention. In one group of eighteen patients with no or trace aortic regurgitation, mean AVA rose from 0.6 to 0.7 cm^2 ($p=9.8x10^{-7}$ according to my calculations)[41]. Thirteen of these patients experienced increase of 0.1 to 0.4 cm^2 with six cross-overs from critical to non-critical values. In another group of 20 patients with isolate aortic stenosis, mean AVAs rose significantly from 0.76 to 0.88 cm^2 ($p=8.2x10-5$)[39]. Seventeen of 20 patients exhibited the rise (increments of 0.06 to 0.34 cm^2). Yet in only one case did the AVA change from critical to non-critical. In the present study, all patients had non-critical values recorded in both resting and intervention states; hence no cross-over occurred, suggesting that the small intervention increase is seldom clinically important.

The fact that all AVAs in the present series were non-critical values raises a question about selection bias, and whether it could have contributed to the finding of statistical

significance. According to considerations outlined in the introduction, possible sources of error in valve area calculations concern the presence of small gradients and the presence of regurgitation. It would be difficult to attribute the area increase to an error involving the intervention enlargement of small gradients and flows when the relatively smaller gradient and flows of the Mitral Stenosis group failed to produce a similar systematic increase in calculated valve area with intervention. As for the matter of regurgitation induced errors, in three of the four patients studied, angiography failed to demonstrate regurgitation.

Other studies in pediatric patients actually demonstrated statistically significant decreases in valve areas with catecholamine infusions, although one may criticize these studies on their failure to exclude subvalvular stenosis and their modification of the orifice equation[53-54]. The apparent increase in AVAs noted in the present study must remain unexplained, but does not appear to be of a magnitude sufficient to alter the clinical interpretation of the severity of the stenosis.

Underlying the use of catecholamines in the catheterization patients with documented regurgitation has been the hope that this kind of intervention would diminish the regurgitant fraction of total flow by increased inotropic and peripheral vasodilatory effects, thereby permitting more precise calculation of valve area. According to the present results,

in three patients with mitral stenosis and mitral regurgitation, intervention did not prove useful.. No cross-over occurred between critical and non-critical values. More data for this group would be desirable

However, in patients with mitral stenosis and aortic regurgitation, catecholamine infusion resulted in critical to non-critical valve area cross-overs in two of five patients. Patient HE experienced a dramatic rise in MVA, from 0.6 to 9.4 cm^2. At operation, no mitral lesion was noted; the recorded resting MVG apparently resulted from the presence of severe aortic regurgitatinn impinging on the mitral valve apparatus. One might wonder if this patient's recorded intervention cardiac output was spuriously high, thereby accounting for the extreme increase in intervention MVA. However, even a seven-fold error in cardiac output determination would have resulted in a valve area cross-over.

The other patient with a valve area cross-over (SP) did not undergo surgery and despite numerous solicitations, did not make herself available for follow-up. Hence one can only speculate that the increase in calculated valve area was secondary to a redistribution of regurgitant flow. An additional patient with critical aortic stenosis (VH) experienced a <u>reduction</u> in mitral valve area despite an operative finding of a normal mitral valve.

Thus, it appears that repeated hemodynamic measurements during an intervention state (in the cases cited, catechol-

amine infusion) does add important information regarding the severity of the mitral lesion in some but not all patients with aortic regurgitation and resting mitral valve gradients. Unfortunately, data are insufficient to delineate which patients in this category of cardiac abnormalities at cath without mitral pathology at operation are likely to a calculated valve area increase with intervention.

Conclusion and Summary

The experience of the Yale-New Haven catheterization laboratory in evaluating patients with left-sided valvular heart disease using the Gorlin formula for the calculation of areas of stenotic valves has been reviewed. Twenty-eight sets of data from 26 patients have been presented, and where applicable, compared to operative cases (11 cases). Specifically, data were analyzed to determine whether exercise or catecholamine infusion undertaken during the catheterization had clinically significant effects on the calculated areas of stenotic valves compared to values obtained during a resting state.

In a group of 18 patients with mitral stenosis and no left-sided regurgitant lesions, the consistency of the Gorlin formula has been reaffirmed in varied hemodynamic settings. Although individual patients exhibited variations in valve areas between the resting and intervention states, the changes were not significant for the group as a whole. Cross-overs from critical to non-critical values occurred in only two patients, both of whom underwent operation in any case. Based on this result, one can conclude that repetition of hemodynamic measurement in this clinical setting does not appear to be useful.

Similarly, in four patients with non-critical resting aortic stenosis, intervention measurements did not alter the impression of the severity of their lesions, but none-

theless, a small but statistically significant increase in calculated areas occurred. This intervention induced area enlargement has been reported by others studying patients with aortic stenosis stressed with exercise. The basis for this enlargement is unclear, and more data will be necessary in order to reach a conclusion concerning the usefulness of intervention measurements in these patients.

In patients with mitral stenosis and aortic regurgitation, but not MS and mitral regurgitation, intervention measurements resulted in a reappraisal of the severity of a suspected mitral lesion in two patients, one of whom was found to have no mitral pathology at subsequent surgery. Intervention measurements appear to be worthwhile in helping to evaluate patients with aortic regurgitation and mitral valve gradients, presumably by altering regurgitant flows.

References

1. Bailey CP: The surgical treatment of mitral stenosis (mitral commisurotomy). Dis Chest 4:377-393, 1949

2. Bailey CP, Glover RP, O'Neill TJE: The surgery of mitral stenosis. J Thorac Surg 19:16-45, 1950

3. Harken DE, Ellis LB, Norman LR: The surgical treatment of mitral stenosis. J Thorac Sur 19:1-15, 1950

4. Janton OH, Glover RP, O'Neill TJE, et al: Results of the surgical treatment for mitral stenosis. Circulation 6:321-333, 1952

5. Janton OH, Heidorn G, Soloff LA, et al: The clinical determination of mitral insufficiency with mitral stenosis. Circulation 10:207-212, 1954

6. Ferrer MI, Harvey RM, Wylie RH, et al: Circulatory effects of mitral commisurotomy with particular reference to selection of patients for surgery. Circulation 12:7-29, 1955

7. Harvey RM, Ferrer MI, Samet P, et al: Mechanical and myocardial factors in rheumatic heart disease with mitral stenosis. Circulation 11:531-551, 1955

8. Grissom R: Acquired heart disease, IntraVascular Catheterization. Edited by HA Zimmerman. Springfield, Ill., Charles C. Thomas, 1959, pp. 379-402

9. Ball JD, Kopelman H, Witham AC: Circulatory changes in mitral stenosis at rest and on exercise. Br Heart J 14: 363-373, 1952

10. Ferrer MI, Harvey RM, Cathcart RT, et al: Hemodynamic studies in rheumatic heart disease. Circulation 6:688-710, 1952

11. Owen SG, Wood P: A new method of determining the degree or absence of mitral obstruction. Br Heart J 17:41-55, 1955

12. Yu PN, Lovejoy FW Jr, Joos HA, et al: Studies of pulmonary hypertension. VI. Am Heart J 49:31-50, 1955

13. Gorlin R, Gorlin SG: Hydraulic formula for calculation of the area of the stenotic mitral valve, other cardiac valvees, and central circulatory shunts. I. Am Heart J 41:1-29, 1951

14. Glenn WWL, Liebow AA, Lindskog, GE: Aortic stenosis and incompetence, in Thoracic and Cardiovascular Surgery, 3rd ed. New York, Appleton-Century-Crofts, 1975, pp. 1020-1053

15. Gorlin R, McMillan IKR, Medd WE, et al: Dynamics of the circulation in aortic valvular disease. Am J Med 18:855-870, 1955

16. Gorlin R: Shunt flows and valve areas, IntraVascular Catheterization, 2nd ed. Edited by HA Zimmerman, Springfield, Ill., Charles C. Thomas, 1966, pp. 545-582

17. Feigenbaum H, Linback RE, Nasser WK: Hemodynamic studies before and after instrumental mitral commisurotomy. Circulation 38:261-276, 1968

18. Rodrigo FA: Estimation of valve area and "valvular resistance." Am Heart J 45:1-12, 1953

19. Hammermeister KE, Murray JA, Blackmon JR: Revision of Gorlin constant for calculation of mitral valve area from left heart pressures. Br Heart J 35:392-396, 1973

20. Cohen MV, Gorlin R: Modified orifice equation for the calculation of mitral valve areas. Am Heart J 84:839-840, 1972

21. Carman GH, Lange RL: Variant hemodynamic patterns in mitral stenosis. Circulation 24:712-719, 1961

22. Alpert JS, Dexter L: Blood flow measurement: The cardiac output, Cardiac Catheterization and Angiography. Edited by W Grossman, Philadelphia, Lea and Febiger, 1974, p.61f

23. Jose AD, Taylor RR, Bernstein L: The influence of arterial pressure on mitral incompetence in man. J Clin Invest 43: 2094-2103, 1964

24. Cohn LH, Mason DT, Ross J Jr, et al: Preoperative assessment of aortic regurgitation in patients with mitral valve disease. Am J Cardiol 19:177-182, 1967

25. Armstrong PW, Dinsmore RE, Harthorne JW, et al: Hemodynamic clues to the discrepancy between the angiographic and intravascular assessment of aortic regurgitation. J Thorac Cardiovasc Surg 66:265-270, 1973

26. Rees JR, Epstein EJ, Criley JM, et al: Hemodynamic effects of severe aortic regurgitation. Br Heart J 26:412-421, 1964

27. Aldridge HE, Lansdown EL, Wigle ED: Diastolic mitral insufficiency. Circulation 42 (Suppl):33-34, 1966

28. Dodge HE, Sandler H, Evans T: Observations on the hemodynamics of severe aortic insufficiency in man. Circulation (abstracts):741, 1960

29. Lochaya S, Igarashi M, Shaffer AB: Late diastolic mitral regurgitation secondary to aortic regurgitation: Its relationship to the Austin-Flint murmur. Am Heart J 74:161-169, 1967

30. Ross J Jr: Application of these principles to the intact heart, Assessment of Cardiac Function. Moderated by E Braunwald. Ann Intern Med 70:369-399, 1969

31. Rushmer RF, Smith O, Franklin D: Mechanisms of cardiac control in exercise. Circ Res 7:602-627, 1959

32. Innes IR, Nickerson M: Norepinephrine, epinephrine, and the sympathomimetic amines, The Pharmacological Basis of Therapeutics, 5th ed. Edited by LS Goodman, A Gilman, New York, MacMillan Publishing Co, 1975, pp. 477-513

33. Krasnow N, Rolett EL, Yurlhak PM, et al: Isoproterenol and cardiovascular performance. Am J Med 37:514-525, 1964

34. Dodge HT, Zoro JD, Sandler H: Cardiovascular effects of isoproterenol in normal subjects and subjects with congestive heart failure. Am Heart J 60:94-105, 1960

35. Ueda H, Machida K, Nakanishi A, et al: Left ventricular performance during the infusion of isoproterenol in patients with valvular heart disease and idiopathic cardiomegaly. Jap Heart J 9:228-240, 1968

36. Nakhjavan FK, Katz MR, Shedrovilzky H, et al: Hemodynamic effects of exercise, catecholamine stimulation, and tachycardia in mitral stenosis and sinus rhythm at comparable heart rates. Am J Cardiol 23:659-666, 1969

37. Levinson GE, Frank MJ, Schwartz CJ: The effect of rest and physical effort on the left ventricular burden in mitral and aortic regurgitation. Am Heart J 80:791-801, 1970

38. Ettinger PO, Frank MJ, Levinson GE: Hemodynamics at rest and during exercise in combined aortic stenosis and insufficiency. Circulation 45:267-276, 1972

39. Bache RJ, Wang Y, Jorgenson CR: Hemodynamic effects of exercise in isolated valvular aortic stenosis. Circulation 44:1003-1013, 1971

40. Goldschlager N, Pfeifer J, Cohn K, et al: The natural history of aortic regurgitation. Am J Med 54:577-588, 1973

41. Anderson FL, Tsagaris TJ, Tikoff G, et al: Hemodynamic effects of exercise in patients with aortic stenosis. Am J Med 46:872-885, 1969

42. Katznelson G, Jreissaty RM, Levinson GE, et al: Combined aortic and mitral stenosis. Am J Med 29:242-256, 1960

43. Lewis RP, Bristow JD, Griswold HE: Exercise hemodynamics in aortic regurgitation. Am Heart J 80:171-176, 1970

44. Lee SJK, Jonsson B, Bevegard S, et al: Hemodynamic changes at rest and during exercise in patients with aortic stenosis of varying severity. Am Heart J 79:318-331, 1970

45. Kloster FE, Bristow JD, Lewis RP, et al: Pharmacodynamic studies in aortic regurgitation. Am J Cardiol 19:644-652, 1967

46. Ross J Jr, Gault JH, Mason DT, et al: Left ventricular performance during muscular exercise in patients with and without cardiac dysfunction. Circulation 34:597-608, 1966

47. Dubin AA, March HW, Cohn K, et al: Longitudinal hemodynamics and clinical study of mitral stenosis. Circulation 44:381-389, 1971

48. Diem K, Lentner C (eds.): Scientific tables, 7th ed. Ardsley, N.Y. Geigy Pharmaceuticals, 1970, p. 260 f

49. Scholander PF: Analyzer for accurate estimation of respiratory gases in one-half cubic centimeter samples. J Biol Chem 167:235-250, 1947

50. Sellers RD, Levy MJ, Amplatz K, et al: Left retrograde angiography in acquired cardiac disease. Am J Cardiol 14: 437-447, 1964

51. McLaurin LP: Resistance to blood flow by vascular beds, Cardiac Catheterization and Angiography. Edited by W Grossman, Philadelphia, Lea and Febiger, 1974, p. 83 f

52. Colton T: Statistics in medicine. Boston, Little, Brown and Co, 1974

53. Neal WA, Lucas RV Jr, Rao S: Comparison of the hemodynamic effects of exercise and isoproterenol infusion in patients with pulmonary valvar stenosis. Circulation 49:948-951, 1974

54. Truccone NJ, Steeg CN, Dell R, et al: Comparison of the cardiocirculatory effects of exercise and isoproterenol in children with pulmonary or aortic valve stenosis. Circulation 56:79-82, 1977

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